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Interpreting adverse drug reaction (ADR) reports as hospital patient safety incidents

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Adverse drug reactions (ADRs) are a reporting category in the National Patient Safety Agency (NPSA) incident reporting system, though the Medicines and Healthcare Products Regulatory Agency (MHRA) pharmacovigilance system is the more established method for collecting ADR data.

WHAT THIS STUDY ADDS

- The majority of ADRs were shown to be of moderate risk to the patient, though some have a severe or catastrophic impact. Classification and reporting of ADRs according to NPSA guidance is possible but offers limited additional value to efforts to improve patient safety over and above the Yellow Card Scheme.

AIM

In the UK, the National Patient Safety Agency (NPSA) includes adverse drug reactions as a reporting category, while the MHRA Yellow Card Scheme also collects data regarding adverse drug reactions (ADRs). In this study, we aimed to assess ADRs using NPSA criteria and discuss the resulting implications.

METHODS

ADRs identified in a 6-month prospective study of 3695 inpatient episodes were assessed according to their impact on the patient and on the organization, using tools developed by the NPSA.

RESULTS

Seven hundred and thirty-three (100%) ADRs were assessed. In terms of impact on the patient, 537 (73.3%) were categorized as 'low' (minor treatment), 181 (24.7%) as 'moderate' (moderate increase in treatment, no permanent harm), 14 (1.91%) as 'severe' (permanent harm) and 1 (0.14%) was categorized as 'catastrophic' (direct cause of death). In terms of impact on the organization, none was categorized as 'no harm/ no risk', 508 (69.3%) as 'insignificant', 188 (25.6%) as 'minor', 25 (3.4%) as 'moderate', 12 (1.6%) as 'major' and none was classed as 'catastrophic'. Less than 2% of ADRs would be eligible for detailed analysis according to the NPSA guidance. The ADRs that cause incidents of greater significance relate to bleeding, renal impairment and *Clostridium difficile* infection.

CONCLUSIONS

Classification of ADRs according to NPSA guidance offers limited additional value over and above that offered by the Yellow Card System. A consistent message needs to be sent to prospective reporters of ADRs; the availability of more than one system is likely to confuse reporters and does not aid patient safety.

Introduction

The National Patient Safety Agency (NPSA) was set up in 2001 following the reports,'*An Organisation with a Memory*' [1] and '*Building a Safer NHS for Patients*' [2], to collect and analyse information on adverse events in the NHS, identify risk factors and provide solutions to improve patient safety [3, 4]. Estimates of the incidence of hospital patient safety incidents vary considerably [5] . Some reports have suggested that approximately 11% of patients experience an adverse event in hospital [3, 6, 7].

The NPSA have defined a patient safety incident as 'any unintended or unexpected incident which could have or did lead to harm for one or more patients receiving NHS care' [8]. ADRs clearly fit within the scope of this definition. The NPSA includes adverse drug reactions (ADRs) as a reporting category [9, 10] although '*Safety in doses: medication safety incidents in the NHS 2007*' [11], states that:

Where medicine has caused harm to a patient but no error took place, the incident is judged to be 'non-preventable' and is usually called an adverse drug reaction (ADR). For example, a patient experiencing a side effect to a medicine for the first time, which could not have been predicted. Data on ADRs are not collected by the NPSA, but these should be reported to the MHRA (Medicines and Healthcare Products Regulatory Agency) Pharmacovigilance 'Yellow Card' System.

This interpretation of an ADR contrasts with those from the ADR literature which include both preventable and non-preventable ADRs. The most frequently cited definition of ADR was established by the World Health Organisation in 1972: 'A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function' [12]. Increasingly, an updated version from Edwards & Aronson is in use, which excludes mild reactions not requiring any intervention, but again makes no reference to preventability:'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product' [13].

Multiple definitions are likely to cause confusion amongst reporters, further highlighted by the fact that the NPSA report [11] uses data from ADR studies [14, 15] and has ADRs as a reporting category. Indeed, over 70% of the ADRs identified in one ADR admission study were categorized as either 'definitely' or 'possibly' avoidable [14]; the NPSA does not explicitly distinguish between the two.

Since ADRs are frequent in our hospitals, and they contribute adversely to patient safety, we have undertaken the opportunity to classify ADRs identified in an in-patient prospective study of 3695 patient episodes [16] according to the NPSA grading systems [17, 18] and to discuss the consequences of applying this classification. For 'low' and 'moderate' impact incidents, the NPSA advises that organizations should record data, investigate demographics and contributory factors when possible, and conduct root-cause analysis where themes emerge. For 'severe' and 'catastrophic' incidents, root-cause analysis including involvement of the patient or carer should be conducted [17].

Methods

All 733 adverse drug reactions, as defined by Edwards & Aronson [13] identified in a 6-month prospective study of 3695 inpatient episodes [16] were assessed according to causality, severity and avoidability algorithms from the ADR literature [19–21] as well as eligibility for reporting to the MHRA [22]. The adverse drug reactions were reclassified by a research pharmacist (ED) as patient safety incidents. The impact on the patient according to the 'Seven Steps to Patient Safety' document criteria is shown in Table 1 [17].

In terms of organizational impact, the ADRs were reassessed according to the 'Doing Less Harm' document [18].The organizational impact risk matrix showing 'poten-

Table 1

NPSA terms and definitions for grading patient safety incidents [17]

Term	Definition
No harm: Impact prevented	Any patient safety incident that had the potential to cause harm but was prevented, resulting in no harm to people receiving NHS-funded care
No harm: Impact not prevented	Any patient safety incident that ran to completion but no harm occurred to people receiving NHS funded care
Low	Any patient safety incident that required extra observation or minor treatment and caused minimal harm, to one or more persons receiving NHS-funded care
Moderate	Any patient safety incident that resulted in a moderate increase in treatment and which caused significant but not permanent harm, to one or more persons receiving NHS-funded care
Severe	Any patient safety incident that appears to have resulted in permanent harm to one or more persons receiving NHS-funded care
Death	Any patient safety incident that directly resulted in the death of one or more persons receiving NHS funded care

tial future risk to the patients and the organization' employs a four-level traffic light system based on likelihood of recurrence and consequences of the event if the incident were to recur (Table 2). 'Doing Less Harm' [18] was a draft document, superseded by 'Seven Steps to Patient Safety [17], and the NPSA do not require the impact on the organization to be reported due to poor reproducibility [23]. However, many organizations continue to use risk matrix grading systems, and therefore we also assessed the ADRs against these criteria.

The study protocol was assessed and approved by the Liverpool Local Research Ethics Committee and the audit department at the Royal Liverpool University Hospital, and the Research Ethics Committee at Liverpool John Moores University.

Results

Seven hundred and thirty-three (100%) ADRs were assessed, with 401 (54.7%) ADRs being definitely or possibly avoidable, and 226 (30.1%) reportable to the MHRA [16]. The impact on the patient according to NPSA criteria [17] is shown in Table 3. Most ADRs clearly have a low impact on the patient, although just under a quarter still required yellow cards, largely for those ADRs involving newer 'black triangle' drugs where all ADRs should be reported.

Of the 14 'severe' ADRs, one was prednisolone-induced diabetes mellitus and thirteen were linked to deaths, with drug-induced renal impairment ($n = 7$), *Clostridium difficile* infection ($n = 5$), and ischaemic bowel ($n = 1$) as contributory factors. The 'catastrophic' ADR was directly related to a drug-induced gastrointestinal bleed. The impact of the ADRs on the organization is shown in Table 4 [18]. It can be seen again that the vast majority of ADRs were classified as minor but many of these had a significant impact on the organization in terms of additional bed days required to treat affected patients.

By definition [18], there were no ADRs that caused 'no harm' and all ADRs were recognized from the British National Formulary (BNF) [24] or Summary of Product Characteristics [25] for each product and therefore likely to recur at some point. Consequently, none of the ADRs was classified as 'green' or 'very low risk' (see Table 2).

The ten most frequent ADRs and their organizational impact are shown in Table 5. From the results, it is clear that the ADRs that cause incidents of greater significance related to bleeding, renal impairment and *Clostridium difficile* infection.

Discussion

It was possible to classify all ADRs included in this study according to NPSA guidance for classifying patient safety

Table 2
Potential future risk to patients and the organization [18]

Likelihood	Consequence Insignificant 'None: No harm/ no risk'	Minor 'Minimal impact'	Moderate 'Increased length of stay (LoS)/ Level of care 1–7 days'	Major: 'Increased LoS/Level of care 8–15 days'	Catastrophic 'International adverse publicity, extended service closure'
Almost certain **'Will undoubtedly recur, possibly frequently'**	Yellow	Yellow	Orange	Red	Red
Likely **'Will probably, but it is not a persistent issue'**	Yellow	Yellow	Orange	Red	Red
Possible **'May recur occasionally'**	Green	Yellow	Orange	Red	Red
Unlikely **'Do not expect it to happen again but it is possible'**	Green	Green	Yellow	Orange	Red
Rare **'Can't believe that this will ever happen again'**	Green	Green	Yellow	Orange	Red

NB: Risk: green = very low; yellow = low; amber = moderate; red = high.

Table 3

Impact of ADRs on patient

Impact on patient	Number of ADRs (n = 733)	Number of Yellow Cards (n = 226)
Low (minor treatment)	537 (73.3%)	53 (23.5%)
Moderate (moderate increase in treatment, no permanent harm)	181 (24.7%)	158 (69.9%)
Severe (permanent harm)	14 (1.91%)	14 (6.2%)
Catastrophic (direct cause of death)	1 (0.14%)	1 (0.4%)

Table 4

Impact of ADRs on the organization

Impact on organization	Number of ADRs (n = 733)	Potential future risk
None: No harm/ no risk	0 (0.0%)	Very low (green)
Insignificant: Minimal impact	508 (69.3%)	Low (yellow)
Minor: Increased length of stay (LoS)/Level of care 1–7 days	188 (25.6%)	Low (yellow)
Moderate: Increased LoS/Level of care 8–15 days	25 (3.4%)	Moderate (amber)
Major: Increased LoS/ Level of care >15 days	12 (1.6%)	High (red)
Catastrophic: International adverse publicity, extended service closure	0 (0.0%)	High (red)

Table 5

Most frequent ADRs and organizational impact

ADR	Impact on organization Insignificant	Minor	Moderate	Major	Yellow Cards
Electrolyte disturbances (n = 168)	147 (87.5%)	19 (11.3%)	2 (1.2%)	0 (0.0%)	27 (18.4%)
Constipation (n = 100)	79 (79.0%)	19 (19.0%)	2 (2.0%)	0 (0.0%)	18 (18.0%)
Increased INR (n = 54)	40 (74.1%)	14 (25.9%)	0 (0.0%)	0 (0.0%)	11 (20.4%)
Bleeding (n = 53)	21 (39.6%)	22 (41.5%)	8 (15.1%)	2 (3.8%)	38 (71.7%)
Renal impairment (n = 45)	21 (46.7%)	18 (40.0%)	4 (8.9%)	2 (4.4%)	33 (73.3%)
Hypotension (n = 35)	29 (82.9%)	6 (17.1%)	0 (0.0%)	0 (0.0%)	8 (27.6%)
Candidal infection (n = 33)	32 (97.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypoglycaemia (n = 32)	18 (56.3%)	12 (37.5%)	0 (0.0%)	2 (6.2%)	14 (43.8%)
Nausea (n = 29)	23 (79.3%)	6 (20.7%)	0 (0.0%)	0 (0.0%)	5 (17.2%)
***Clostridium difficile* infection (n = 25)**	0 (0.0%)	18 (72.0%)	3 (12.0%)	4 (16.0%)	19 (76.0%)

incidents. Individual ADRs generally had little impact on the patient or the organization. Collectively, all ADRs were graded 'yellow' to 'red', i.e. none was 'green' in the traffic-light risk grading system in terms of future risk of recurrence, with more serious ADRs logically resulting in a greater potential impact on the individual and the organization.

Since spontaneous ADR reporting rates are low [26] a number of opportunities to learn from preventable ADRs may be lost. Root-cause analysis of ADRs may provide new strategies for reducing the burden of ADRs and responding to serious ADRs, e.g. rapid referral or closer monitoring. Perhaps the most important issue raised in this study is that, according to guidelines from the Seven Steps to Patient Safety document, severe or catastrophic incidents should be analysed using root-cause analysis [17]. However, the results of this study reported in Table 3 suggest that, trends apart, root-cause analysis would only be necessary for 2% of identified ADRs. Thus, although we might learn from root-cause analysis of major or catastrophic events, the overall value of using a patient-safety incident reporting system for all ADRs over and above that of the Yellow Card Scheme for ADRs is therefore questionable. Were large numbers of ADRs to be analysed using this technique, opportunities to identify new interventions to prevent serious ADRs could be identified through the pooling of data on a national level. Root-cause analysis may be useful to identify potential 'system-failures' surrounding ADRs and their occurrence, and potential problems in the medicines management system which may contribute to preventable ADRs. Current pooling of Yellow Card data by the MHRA does not allow for detailed assess-

ment of the individual circumstances surrounding ADRs, which may be possible if the risk-management teams of the NHS Trusts involved assessed each 'severe' or 'catastrophic' ADR. Root-cause analysis of serious incidents would involve senior management teams, risk management groups, patients and carers. Involvement of these parties would inevitably make the ADR issue more political, but may also highlight the burden of ADRs, potentially allowing more resources to be allocated to reducing the ADR burden. However, given the fact that ADRs are common, and root cause analyses are resource-intensive, the uptake is likely to be low.

Although ADRs are a common occurrence, affecting approximately 15% of inpatient episodes and causing 6.5% of admissions [14, 16], the majority of ADRs had little impact on the patient or the organization according to the categorization recommended by the NPSA. This categorization is recommended to enable prompt reporting from the practitioner but is a clear limitation of this classification as it ignores aspects of the patient perspective, including effects on quality of life and length of stay. Indeed, 25% of ADRs identified in the original study [16] increased the length of stay or level of care. As hospitals are increasingly remunerated for their activity in terms of patient care, in addition to the impact on the patient, this represents a significant financial burden.

Consistent with the incidence of hospital acquired infections and the publicity surrounding this, it is important to note that *C. difficile* infection provided the highest number of incidents with a major impact on organizations. This is illustrated by the recent Maidstone and Tunbridge Wells reports which received a significant level of publicity both in the medical and general media [27, 28].

ADR definitions are inconsistent, with the NPSA asserting that ADRs are not preventable [10], leaving approximately 50% of the ADRs from this study classifiable by the NPSA as medication errors and not ADRs, although the definition of medication errors also varies greatly [29].

It is unclear from the NPSA criteria as to whether possibly and definitely avoidable ADRs should be treated in the same manner, and it should be acknowledged that there is likely to be great variation in defining a 'preventable' ADR, even when using published guidance such as the Hallas criteria [21]. Given this ambiguity, it seems inappropriate to ask the reporter or coder to make judgements of avoidability before deciding where to report the ADR. Collation of data of ADRs currently perceived as unavoidable is also important, as assessment of trends in the types of patients experiencing these ADRs may, in the future, contribute to a method for avoiding these ADRs.

In summary, the different definitions used by the NPSA and MHRA are likely to lead to confusion which may deter potential reporters. If both systems are to co-exist for ADR reporting, it is important that the NPSA and MHRA work together [10]. In July 2009, a letter was issued jointly from the NPSA and MHRA to NHS Trust Chief Executives stating that the MHRA and the NPSA's National Reporting and Learning Service had formalized an agreement to share data held by the organizations and that there was a longer term goal for developing a single reporting portal suitable for both organizations [30]. The NPSA website now also clearly states that ADRs should be reported to the MHRA [31], although by stating in their letter that 'patient safety incidents which could have, or did lead to harm to one or more patients receiving NHS care should continue to be reported to the NPSA' [32], ambiguity still remains, as ADRs can clearly cause harm.

The nature of the two organizations is clearly different, though both fundamentally have the aim of improving patient safety at their core; ADRs form only a small part of the dataset which the NPSA aims to collect. Classification of ADRs according to NPSA guidance offers a different perspective on the impact of ADRs. However, our analysis shows that this currently has limited additional value over and above that offered by the Yellow Card system. Furthermore, while the NPSA has published a number of patient safety alerts based on very few reports of patient deaths [32, 33] it has yet to tackle ADRs, which cause hundreds (or thousands) of deaths each year in the UK alone, in a substantial way.

In conclusion, therefore, it is important that a consistent message is sent out to prospective reporters of the need for reporting using established systems (e.g. Yellow Cards) and the need for continued vigilance in prescribing rationally, and preventing and detecting ADRs. Whether the NPSA system can provide something that the MHRA cannot is unclear, as NPSA methods such as root-cause analysis, though potentially helpful, would only be applied to a very small proportion of ADRs, and promotion of dual methods for this purpose may undermine reporting through the established Yellow Card system.

Competing interests

MP is a member of the Commission on Human Medicines and chairs its Pharmacovigilance Expert Advisory Group. The other authors have no competing interests. The views expressed in this article are entirely those of the authors, and do not represent the views of any organisations that they represent.

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